

**CLAIMS**

1. Method to produce an IL-11 agonist, which comprises producing a protein having the sequence of an IL-11 mutein that is derivable from a wild-type IL-11 sequence by replacement of at least two non-hydrophobic amino acids within the epitope for IL-11R $\alpha$  by hydrophobic ones.
2. IL-11 mutein, the sequence of which comprises a sequence which is derivable from the complete sequence of a wild-type IL-11:
- 10       - by replacement of the hydrophilic amino acids at positions 182 and 186 (positions computed by reference to the complete wild-type sequence) by X<sub>1</sub> and X<sub>2</sub> respectively, X<sub>1</sub> and X<sub>2</sub> being chosen from the group comprising:
- Valine (symbol = V or Val),
  - Alanine (symbol = A or Ala),
  - 15       ○ Proline (symbol = P or Pro),
  - Leucine (symbol = L or Leu),
  - Isoleucine (symbol = I or Ile),
  - Phenylalanine (symbol = F or Phe),
  - Methionine (symbol = M or Met), and
  - 20       ○ Tryptophan (symbol = W or Trp),
- and by deletion of a N-terminal portion that does not exceed the first 34 N-terminal amino acids.
3. IL-11 mutein of claim 2, characterized in that said wild-type IL-11 has the sequence of a human IL-11, or of a macaque IL-11, or of a mouse IL-11, or of a rat IL-11.
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4. IL-11 mutein of claim 2 or 3, the sequence of which comprises a sequence chosen from the group comprising SEQ ID NO:9, SEQ ID NO:24, SEQ ID NO:39, SEQ ID NO:54, and the conservative variant sequences thereof, wherein said conservative variant sequences are of at least 80%, preferably at least 90% identity with at least one of SEQ ID NO:9, SEQ ID NO:24, SEQ ID NO:39, or SEQ ID NO:54, provided that X<sub>1</sub>
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and X<sub>2</sub> are still as defined in claim 2, and provided that the resulting variant protein has retained the ability to induce proliferation of an IL-11 dependent cell line.

5 5. IL-11 mutein according to any one of claims 2-4, characterized in that X<sub>1</sub> and X<sub>2</sub> are V or A.

6. IL-11 mutein according to any one of claims 2-5, characterized in that X<sub>1</sub>=V and X<sub>2</sub>=A.

10 7. IL-11 mutein of claim 6, characterized in that it comprises a sequence of SEQ ID NO:10, or of SEQ ID NO:25, or of SEQ ID NO:40, or of SEQ ID NO:55.

8. IL-11 mutein according to any one of claims 2-5, characterized in that X<sub>1</sub>=A and X<sub>2</sub>=V.

15 9. IL-11 mutein of claim 8, characterized in that it comprises a sequence of SEQ ID NO:11, of SEQ ID NO:26, of SEQ ID NO:41, or of SEQ ID NO:56.

20 10. IL-11 mutein according to any one of claims 2-5, characterized in that X<sub>1</sub>=V and X<sub>2</sub>=V.

11. IL-11 mutein of claim 10, characterized in that it comprises a sequence of SEQ ID NO:12, of SEQ ID NO:27, of SEQ ID NO:42, or of SEQ ID NO:57.

25 12. IL-11 mutein according to any one of claims 2-5, characterized in that X<sub>1</sub>=A and X<sub>2</sub>=A.

13. IL-11 mutein of claim 12, characterized in that it comprises a sequence of SEQ ID NO:13, of SEQ ID NO:28, of SEQ ID NO:43, or of SEQ ID NO:58.

30 14. IL-11 mutein according to any one of claims 2-13, characterized in that it comprises a sequence which is derivable from the complete sequence of a wild-type IL-11:

- by replacement of the hydrophilic amino acids in positions 182 and 186 (positions computed by reference to the complete wild-type sequence) by  $X_1$  and  $X_2$  respectively,  $X_1$  and  $X_2$  being as defined in claim 2, and

- by deletion of the first 21 N-terminal amino acids.

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15. IL-11 mutein according to claim 14, characterized in that it comprises a sequence of SEQ ID NO:14, SEQ ID NO:29, SEQ ID NO:44 or SEQ ID NO:59, wherein  $X_1$  and  $X_2$  are defined in claim 2.

10 16. IL-11 mutein according to claim 15, characterized in that  $X_1$ =V and  $X_2$ =A.

17. IL-11 mutein according to claim 16, characterized in that it comprises a sequence of SEQ ID NO:15, or of SEQ ID NO:30, or of SEQ ID NO:45, or of SEQ ID NO:60.

15 18. IL-11 mutein according to claim 15, characterized in that  $X_1$ =A and  $X_2$ =V.

19. IL-11 mutein according to claim 16, characterized in that it comprises a sequence of SEQ ID NO:16, or of SEQ ID NO:31, or of SEQ ID NO:46, or of SEQ ID NO:61.

20 20. IL-11 mutein according to claim 15, characterized in that  $X_1$ =V and  $X_2$ =V.

21. IL-11 mutein according to claim 20, characterized in that it comprises a sequence of SEQ ID NO:17, or of SEQ ID NO:32, or of SEQ ID NO:47, or of SEQ ID NO:62.

25 22. IL-11 mutein according to claim 15, characterized in that  $X_1$ =A and  $X_2$ =A.

23. IL-11 mutein according to claim 22, characterized in that it comprises a sequence of SEQ ID NO:18, or of SEQ ID NO:33, or of SEQ ID NO:48, or of SEQ ID NO:63.

30 24. IL-11 mutein according to any one of claims 2-23, characterized in that it comprises a sequence which is derivable from the complete sequence of a wild-type IL-11, by replacement of the hydrophilic amino acids in positions 182 and 186 (positions

computed by reference to the complete wild-type sequence) by  $X_1$  and  $X_2$  respectively,  $X_1$  and  $X_2$  being as defined in claim 2.

25. IL-11 mutein according to claim 24, characterized in that it comprises a sequence of  
5 SEQ ID NO:19, or of SEQ ID NO:34, or of SEQ ID NO:49, or of SEQ ID NO:64,  
wherein  $X_1$  and  $X_2$  are as defined in claim 2.

26. IL-11 mutein according to claim 24, characterized in that  $X_1=V$  and  $X_2=A$ .

10 27. IL-11 mutein according to claim 26, characterized in that it comprises a sequence of  
SEQ ID NO:20, or of SEQ ID NO:35, or of SEQ ID NO:50, or of SEQ ID NO:65.

28. IL-11 mutein according to claim 24, characterized in that  $X_1=A$  and  $X_2=V$ .

15 29. IL-11 mutein according to claim 28, characterized in that it comprises a sequence of  
SEQ ID NO:21, or of SEQ ID NO:36, or of SEQ ID NO:51, or of SEQ ID NO:66.

30. IL-11 mutein according to claim 24, characterized in that  $X_1=V$  and  $X_2=V$ .

20 31. IL-11 mutein according to claim 30, characterized in that it comprises a sequence of  
SEQ ID NO:22, or of SEQ ID NO:37, or of SEQ ID NO:52, or of SEQ ID NO:67.

32. IL-11 mutein according to claim 24, characterized in that  $X_1=A$  and  $X_2=A$ .

25 33. IL-11 mutein according to claim 32, characterized in that it comprises a sequence of  
SEQ ID NO:23, or of SEQ ID NO:38, or of SEQ ID NO:53, or of SEQ ID NO:68.

34. Nucleic acid, characterized in that its sequence codes for a mutein according to any  
one of claims 2-33.

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35. Nucleic acid according to claim 34, characterized in that it comprises the sequence  
of SEQ ID NO:72, wherein each of  $n_1n_2n_3$  and  $n_4n_5n_6$  codes for:

- 5      ○ Valine (symbol = V or Val), or  
        ○ Alanine (symbol = A or Ala), or  
        ○ Proline (symbol = P or Pro), or  
        ○ Leucine (symbol = L or Leu), or  
        ○ Isoleucine (symbol = I or Ile), or  
        ○ Phenylalanine (symbol = F or Phe), or  
        ○ Methionine (symbol = M or Met), or  
        ○ Tryptophan (symbol = W or Trp).
- 10    36. Nucleic acid according to any one claims 34-35, characterized in that it comprises the sequence of SEQ ID NO:72, wherein  $n_1n_2n_3$  and  $n_4n_5n_6$  are both selected from the group comprising the following codons:
- 15      - GCT, GCC, GCA, GCG,  
        - GTT, GTC, GTA, GTG,  
        - TTA, TTG, CTT, CTC, CTA, CTG,  
        - ATT, ATC, ATA,  
        - TTT, TTC,  
        - ATG,  
        - CCT, CCC, CCA, CCG,  
20      - TGG.
- 25    37. Nucleic acid according to any one of claims 34-36, characterized in that it comprises the sequence of SEQ ID NO:71 or of SEQ ID NO:70, wherein the codons  $n_1n_2n_3$  and  $n_4n_5n_6$  are as defined in any one of claims 35-36.
38. Nucleic acid according to any one of claims 34-36, characterized in that it comprises the sequence of SEQ ID NO:76 or of SEQ ID NO:74, wherein the codons  $n_1n_2n_3$  and  $n_4n_5n_6$  are as defined in any one of claims 35-36.
- 30    39. Nucleic acid according to any one claims 34-35, characterized in that it has the RNA sequence of SEQ ID NO:75, wherein the codons  $n_1n_2n_3$  and  $n_4n_5n_6$  are both selected from the group comprising the following codons:

- GCU, GCC, GCA, GCG
  - GUU, GUC, GUA, GUG,
  - UUA, UUG, CUU, CUC, CUA, CUG,
  - AUU, AUC, AUA,
  - 5 - UUU, UUC,
  - AUG,
  - CCU, CCC, CCA, CCG,
  - UGG.
- 10 40. Transfection vector, characterized in that it comprises a nucleic acid according to any one of claims 34-39.
41. Transfection vector according to claim 40, characterized in that it further comprises a nucleotide sequence coding for a Flag tag.
- 15 42. Transfection vector according to any one of claims 40-41, characterized in that it comprises the sequence of SEQ ID NO:79, wherein  $n_1n_2n_3$  and  $n_4n_5n_6$  are as defined in claim 35.
- 20 43. Cell, characterized in that it comprises a nucleic acid according to any one of claims 34-39, and/or which has been transfected by a transfection vector according to any one of claims 40-42, and/or which express a mutein according to any one of claims 2-33.
44. Drug characterized in that it comprises:
- 25 - a therapeutically effective amount of an IL-11 mutein according to any one of claims 2-33, or of a nucleic acid according to any one claims 34-39, or of a transfection vector according to any one of claims 40-42, or of a cell according to claim 43,
- and, optionally, a pharmaceutically-acceptable vehicle.
- 30 45. Drug according to claim 44, characterized in that it is intended for the prevention or treatment of an inflammatory disease or condition.

46. Drug according to any one claims 44-45, characterized in that it is intended for the prevention or treatment of a septic shock.
47. Drug according to any one claims 44-45, characterized in that it is intended for the prevention or treatment of diabetes.
48. Drug according to any one claims 44-47, characterized in that it is intended for inhibiting microvascular endothelium apoptosis.
49. Drug according to claim 44, characterized in that it is an anti-thrombocytopenia drug.